

Iron status and brain function: serum ferritin levels associated with asymmetries of cortical electrophysiology and cognitive performance^{1,2}

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ABSTRACT Levels of serum ferritin and iron were examined in relation to cognitive performance and quantitative EEG measures in 69 normal university students. Higher levels of serum ferritin were associated with greater activation of the left hemisphere relative to the right, indicated by less power in the EEG spectra from left hemisphere electrodes. Iron status was significantly related to cognitive performance on two of the cognitive tasks, and these relationships were consistent with the EEG asymmetries: higher ferritin predicted greater verbal fluency but poorer nonverbal auditory task performance. These results suggest that body iron stores are relevant to specific neurophysiological processes supporting attention. *Am J Clin Nutr* 1984;39:105-113.

KEY WORDS Iron nutrition, ferritin, brain function, EEG, cognition, dopamine, human

Introduction

Iron-deficiency anemia was apparently a recognized illness in ancient Egypt and was known to Hippocrates (1). Chlorosis, named the "green sickness" because of the pallor it produced, was found in the 17th century to be responsive to iron therapy (1). Since its recognition in the medical literature, iron deficiency has been thought to be associated with psychological symptoms, but clear evidence has been elusive. Given the current prevalence of iron deficiency (2), definition of the relationship between iron nutriture and psychological function could be of major importance. Problems in characterizing the neuropsychological effects of iron deficiency have been both theoretical and methodological. Without some knowledge of the role of iron in the brain, attempts to document psychological effects of iron deficiency must resort to nonspecific and thus insensitive measures. Although recent studies have provided evidence that in children there are measurable cognitive effects of iron deficiency (2-4), the particular features of attention or cognition that are impaired remain to be determined (5).

Research with iron deficiency in animals

has suggested that an impairment of dopaminergic neurotransmission may underlie the frequently observed decrement in behavior activity (5-7). This hypothesis is consistent with the concentration of iron in brain dopamine pathways (8) and may suggest the involvement of specific attentional control systems dependent on dopaminergic pathways that mediate the cognitive impairment in iron-deficient humans.

Current models of the neural systems controlling attention (9, 10) point to the importance of the brain's self-regulation of its activation level as a function of the demands for cognitive activity. The simultaneous determination of cortical activation and cognitive performance may allow a precision of neuropsychological measurement not pos-

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Received April 11, 1983.

Accepted for publication August 9, 1983.

sible with conventional psychometrics, and should be directly relevant to the function of the neurotransmitter systems modulating neural activation. We have applied measures of cortical electrophysiology and cognitive performance to examine the role of iron nutriture in attentional processes.

In an initial study (11), iron status was found to covary with a number of EEG variables, although no significant relationships were found with cognitive performance. The pattern of the EEG findings indicated that power in the δ band (0.5 to 3.5 Hz) was higher for subjects with lower iron status, possibly indicating less alertness during the experimental procedure. In addition, many of the relationships of EEG power with iron status were asymmetric, with less power (greater activation) in the left hemisphere associated with higher serum ferritin and iron levels. Although the small sample size of this study causes any inferences to be tentative, a second cross-sectional study with evoked potential measures also indicated that left hemisphere activation, reflected by higher amplitude evoked potentials in left posterior electrodes, was predicted by higher serum ferritin (12). In a subsequent 6-month longitudinal study of seven men (13), we examined whether EEG and cognitive performance measures would reflect the decrement in iron status caused by repeated blood sampling. Although the findings showed substantial individual variability, and the δ frequency data were not as predominant as in the earlier cross-sectional study, in four of the seven men asymmetric regression coefficients from the two hemispheres were observed that were consistent with the previous cross-sectional study.

The major difficulty with these initial studies is their small sample sizes. It appears that the patterning of the EEG data is important to iron status, but to perform the multivariate analyses required to determine this patterning with any confidence requires a larger sample. The present research was conducted to examine further the relation between iron status and cortical activation during cognitive effort, to find if the results of the exploratory studies could be reproduced and thus be generalized to the population. An important question was whether

measures of cognitive performance ability would show a relationship to iron status. Although it may be argued that electrophysiological measures are more sensitive than performance measures, an absence of an effect on psychological performance would cast doubt on the practical significance of the relation between cortical activation and iron nutriture observed in the earlier studies. In addition, because the earlier findings pertain to iron status in normal persons and not to iron deficiency, an important issue is whether indices of iron status may also index some other physiological attribute that covaries with brain function. Since animal studies have suggested that hepatic ferritin is influenced by thyroid activity (14), and thyroid function in turn influences cortical arousal (15, 16), we examined measures of thyroid function in the present study to find if these might provide an alternative explanation for the apparent relationship between iron status and brain function.

Materials and methods

This study was approved by the human studies committee of the University of North Dakota and the United States Department of Agriculture. University students were recruited from introductory psychology courses for research on nutrition and brain function. The students were offered 10 dollars and course credit for participation. Usable data were collected on 17 males and 52 females. Since our previous studies indicated a relation between iron nutriture and brain lateralization, e.g., Tucker & Sandstead (11, 12), only right-handed subjects were recruited. When the subject reported to the laboratory a trained technician applied the EEG electrodes and data were collected during a 30-s, eyes-closed resting period and while performing the battery of eight cognitive tasks described below. During the same week as the EEG recording, a morning blood sample was taken to assess each subject's characteristic level of iron, serum ferritin, and several indices of thyroid function. Subjects were required to fast after the previous day's evening meal until the blood draw.

Cognitive tasks

Six cognitive tasks were performed with the eyes closed. In a task emphasizing imagery, the subject was asked to maintain a clear visual image of a concrete object, such as a lawnmower, for 30 s and then rate the vividness of the image on a 1 to 7 scale. The word fluency task required that the subject generate four words beginning and ending with specified letters for each of six 20-s trials. The pair of letters was verbally presented and the subject pushed a button when ready to respond; performance measures were mean latency to generate the four words and the total number of

correct words. In none of the tasks was EEG data collected during the production of a response, in order to avoid movement or other artifact.

Additional eyes-closed tasks included digit span forward and backward and tonal memory forward and backward. The digit span task followed the procedures of the digit span subtest of the Wechsler Adult Intelligence Scale: the subject was presented with a string of 3 digits at a rate of 1/s, then after a brief pause was requested to repeat the digit string. EEG data were collected in 1-s epochs as the subject listened to the digit string and for the pause interval after the string was presented. After correct performance with a 3-digit string, a 4-digit string was presented, with sequentially longer strings given until failure on two trials successively. For the 3- and 4-digit trials 6 s of EEG data were collected, with 8 s collected for 5- and 6-digit trials, 10 s for the 7- and 8-digit trials, and 12 s for the 9-digit trial if the subject performed sufficiently well to reach that point. For the digit span backward task, the subject was requested to repeat the digit string in reverse order. The presentation was parallel to digits forward, and the number of seconds per trial was equal to twice the number of digits. Since the digits were presented at a rate of 1/s, there was an equal number of seconds as digits after the presentation before the subject was signaled to respond. Most people take longer to respond to digits backward than digits forward because of the additional processing required to organize the response.

For the tonal memory forward task, a sequence of 2 tones was presented, followed by a short pause, then a sequence of 2 more tones; after a short interval the subject was asked whether the 2 sequences of tones were the same or different. After a second 2-tone trial, additional tones were added sequentially with 2 trials at each tone sequence length, up to 6 tones. For the 2- and 3-tone trials, 6 s of EEG data were collected; for longer sequences the number of sec of EEG was twice the number of tones. For the tonal memory backward task the subject was presented with 2 sequences of tones and asked if the second sequence was the same or different than the first sequence played backward. The number of tones per sequence was increased incrementally as with the tonal memory forward, but the longest sequence presented for tonal memory backward was 5 tones rather than 6.

Two additional cognitive tasks were performed with the subject's eyes open. In both the character and shape tasks, a group of letters was displayed in a pattern on a video screen, and the subject was asked to attend either to the identity of the individual characters or the shape of the pattern formed by those characters. After a 2-s interstimulus interval, a second group of letters was displayed and the subject responded whether the two groups were the same or different, with respect to the attribute attended. Performance measures for the character and shape tasks were the number of trials on which the subject was correct in his or her response, and the total latency of correct responses.

EEG recording and analysis

EEG signals were recorded from left and right frontal (F3, F4), temporal (T3, T4), parietal (P3, P4), and occipital (O1, O2) locations, referenced to linked ears

with a vertex ground. After amplification with a 0.1 time constant and analog filtering with a 30 Hz lo-pass filter the signals were digitized at 512 Hz and then 4-point smoothed to yield an effective sampling rate of 128 Hz. One-sec epochs of the raw data were then examined off-line on a display screen and examined for contamination by eye movement, blink, myographic or other artifact. All EEG data collected during the cognitive tasks and the resting condition that were artifact-free were analyzed. After appropriate tapering of the epoch, spectral analysis with the fast Fourier transform produced power spectra with 1.0 Hz resolution. This analysis delineates the power (amplitude squared) in the EEG waveform at each of the frequencies of interest. An example of power spectra computed for successive epochs for a single subject is shown in Figure 1. For each of the δ (1 to 3 Hz), θ (4 to 7 Hz), α (8 to 12 Hz), β 1 (13 to 18 Hz), β 2 (19 to 27 Hz), and β 3 (28 to 50 Hz) bands, mean power for the band was computed for each of the electrode sites for each cognitive task for each subject. A complete description of the EEG analysis techniques is provided elsewhere (11).

Assessment of iron status and thyroid function

Serum ferritin was assayed by competitive binding radioimmunoassay. Iron was determined by atomic absorption spectrophotometry (17). The samples were aspirated directly after dilution with 2% HCl and were compared with standards made up in HCl. Thyroid stimulating hormone was assayed by solid phase second antibody techniques. Thyroxine (T4) and triiodothyronine (T3) were measured by double antibody radioimmunoassay.

Statistical analysis

The covariation between individual measures of iron status and thyroid function, and between those measures and cognitive performance, were examined with zero-order Pearson correlations. Canonical correlations were used to determine the relationship between the multiple measures of iron nutriture and the multiple measures of thyroid function. Canonical analysis simply finds a linear combination for each set of measures, the two resulting linear equations referred to as canonical variables, such that the zero-order correlation between the two canonical variables is maximized. The distributions of the thyroid measures were positively skewed with most values moderately low and a few values quite high. Log transformation of these distributions before statistical analysis yielded distributions that closely approximated the normal.

Due to the positive skew characteristic of distributions of EEG power measures, the EEG data were also log transformed before analysis. For each cognitive task and each frequency band of the EEG, stepwise multiple regressions were run with the eight channels of the EEG as predictors and the measure of iron status (either serum ferritin or serum iron) as the criterion. A set of regressions was also run with each of the thyroid measures as the criterion, to determine if these would parallel the regressions of EEG data on iron status. Finally, for each cognitive task, regressions were run with the EEG data from that task predicting task performance. Regression analysis forms a linear equation combining

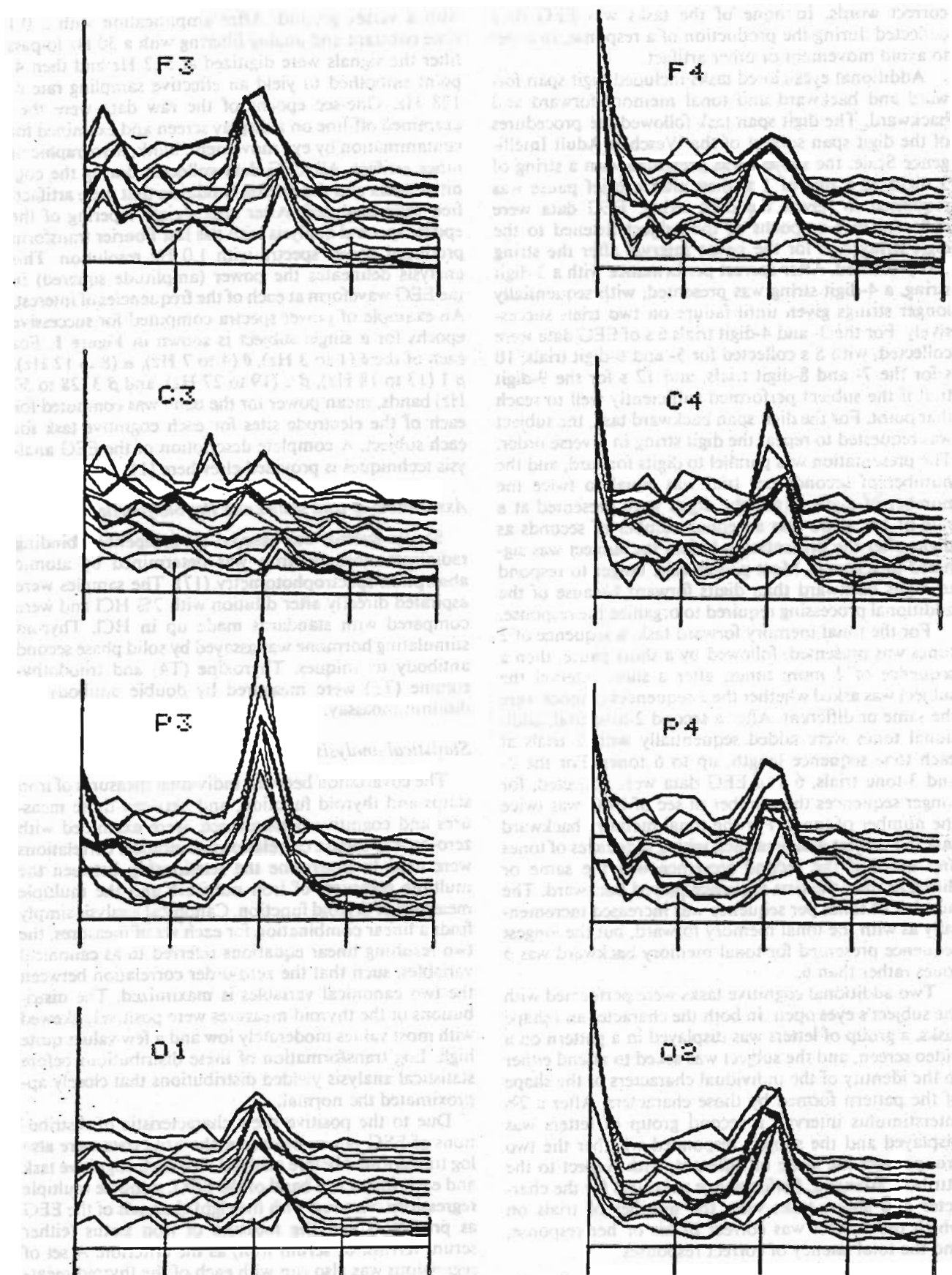


FIG 1. An example of power spectra computed from successive epochs of 8 channels of EEG. The plot for each epoch indicates the power at each of the frequency intervals resolved by the analysis. The increments on the x axis represent 5 Hz frequency intervals. The successive spectra are plotted with a hidden line routine to prevent overwriting previous plots. The peak in the spectra at about 10 Hz reflect the α frequency of the EEG.

the various predictors in a least squares fashion such that the weight or coefficient assigned each predictor reflects its contribution to the prediction model. The linear equation is then used to predict the criterion variables. The stepwise routine used adds predictors to the equation, one at a time, generating the best one-predictor model, two-predictor model, etc., until all predictors are included in the prediction of the criterion. In the analyses reported here, the most parsimonious models were selected to characterize the EEG power-criterion (measures of iron status, thyroid function, and cognitive performance) relationships. Thus, the models chosen invoked the fewest predictors while still accounting for most of the variance explained by the full eight-variable (eight channel) models.

Results

The mean serum ferritin level of the subjects in this sample was 41.8 ng/ml (SD = 28.4). The mean serum iron was 93.8 μ g/dl (SD = 33.0). As in previous research (11, 12) the serum iron and serum ferritin measures of iron status were related ($r = 0.51$, $p < 0.001$).

EEG and iron status

The regressions of EEG data on each of the iron status measures showed stronger relations to ferritin than to iron. Of the 48 regressions run on ferritin (six EEG frequency bands for each of eight cognitive tasks), 39 were significant at the 0.05 level or better (see Table 1). The variance explained by the most parsimonious models ranged from 0.07 to 0.29. As is shown by the regression coefficients in Table 1, there was a definite patterning of the EEG data that predicted the subject's serum ferritin level. Of the 39 left hemisphere predictors retained in the significant models, 37 had negative signs, indicating less left hemisphere power (greater functional activation) was predictive of higher serum ferritin levels. For right hemisphere leads, greater power in the temporal lobe was especially important in the prediction of ferritin level. Less power in both the left and right occipital regions was related to higher ferritin. The right parietal location showed a frequency-specificity in the ferritin regressions, with less power in lower bands and more power in higher frequencies related to higher ferritin levels. When these analyses were inspected for each cognitive task, no clear differentiation among the findings for each task was ob-

served, with results for the resting condition similar to those for the cognitive performance conditions.

Because of the substantial sex differences in ferritin level (with females coded as 0 and males as 1 the correlation with serum ferritin was 0.46, $p < 0.001$), separate regressions were run for the male and female samples. Although somewhat more significant findings appeared for the males, both sexes reflected the patterning of the results of the combined analysis, thus indicating that gender differences could not account for the relation between EEG data and ferritin level.

The regressions of EEG power on serum iron showed only 11 of the 48 regressions to yield significant ($p < 0.05$) models (see Table 2). Of these, however, some specificity was observed; five of the significant models were for the δ frequency with the squared multiple correlations ranging from 0.10 to 0.25. As with the ferritin regressions, we examined the zero-order correlations between the EEG predictor channels and the iron criterion measure to find if the signs of the regression coefficients could be interpreted to reflect direct relations with the criterion (ie, the coefficients were not due to suppressor effects in the regression analysis). Particularly for the frontal lobes, the asymmetry of the regression coefficients was consistent across several tasks, with less power in the left frontal and greater power in the right frontal locations related to higher serum iron. In contrast to the results of our first cross-sectional study (10), there was no particular tendency for serum iron to covary with δ power recorded during the resting condition.

Iron status and cognitive performance

The relations between the iron measures and performance of the cognitive tasks were examined after controlling for gender differences in cognitive task performance (which were significant for the digit span backward, tonal memory forward, shape, and character tasks). These partial correlations showed higher serum ferritin to be associated with poorer performance of the tonal memory backward task ($r = -0.30$, $p < 0.05$). Serum iron was associated with better (shorter latency) performance on the word fluency task ($r = -0.30$, $p < 0.05$).

TABLE 1
Multiple regressions of EEG power on serum ferritin separately
for each frequency band and recording condition
significant ($p < .05$) models only

| Frequency task | Regression coefficients | | | | | | | | R ² |
|----------------|-------------------------|-----|-----|----|-----|-----|-----|-----|----------------|
| | Channel | | | | | | | | |
| | F3 | F4 | T3 | T4 | P3 | P4 | O1 | O2 | |
| δ | | | | | | | | | |
| R | | | | 15 | | | | -37 | 0.10* |
| IMG | | | -48 | 37 | | | | | 0.11* |
| DSF | | | | 25 | | | | -60 | 0.19† |
| DSB | | 28 | | | -78 | | | | 0.19† |
| TMF | | | -47 | 65 | | -48 | | | 0.20† |
| TMB | | | | | | | | -48 | 0.16† |
| WF | | 24 | | | | | | -49 | 0.12* |
| S2 | | | | 34 | | -41 | | -31 | 0.24† |
| C2 | -19 | | | | | | | -29 | 0.16* |
| ϕ | | | | | | | | | |
| DSF | | | -47 | 80 | | -39 | | | 0.24† |
| DSB | | | | 38 | | | | -44 | 0.13* |
| TMF | | | | 72 | | -66 | | | 0.12* |
| WF | | | -36 | 54 | | | | | 0.13* |
| S2 | -88 | 111 | | | -52 | | | | 0.26† |
| C2 | | | | | | -48 | | | 0.10* |
| α | | | | | | | | | |
| DSF | | | | 56 | | | -35 | | 0.20† |
| DSB | 46 | | | | | | -34 | | 0.14* |
| WF | | | -21 | 42 | | -23 | | | 0.16* |
| S2 | | | | | | | -24 | | 0.09* |
| C2 | -30 | | | | | | | | 0.07* |
| β | | | | | | | | | |
| R | | | | 27 | | | | -43 | 0.17† |
| IMG | | | | 42 | | | | | 0.28‡ |
| DSF | | | | 31 | | 42 | -51 | | 0.29§ |
| DSB | | | | | | 54 | -77 | | 0.16† |
| TMF | | | | 18 | | 54 | -81 | | 0.21† |
| TMB | | | | 19 | | 41 | -61 | | 0.18* |
| WF | | | | | | 46 | -65 | | 0.19† |
| S2 | 36 | | | | | | -76 | | 0.22† |
| C2 | | | | 21 | | | -49 | | 0.18† |
| $\beta 2$ | | | | | | | | | |
| R | | | -22 | 30 | | | | -27 | 0.15* |
| IMG | -40 | | | 23 | | 65 | -55 | | 0.26† |
| DSF | | | | 17 | | 36 | -59 | | 0.15* |
| TMF | | | -27 | 28 | | | | | 0.17* |
| TMB | | | -29 | 23 | | | | | 0.12* |
| WF | | | | | | | -39 | | 0.11* |
| C2 | | | | | | | | -27 | 0.08* |
| $\beta 3$ | | | | | | | | | |
| R | -24 | | | 15 | | | | -21 | 0.14* |
| IMG | -50 | | | | | 78 | -53 | | 0.29§ |
| DSF | -26 | | | | -75 | 152 | | -44 | 0.22* |
| DSB | -32 | | | | -59 | 122 | | -29 | 0.17* |
| TMF | -34 | | | 11 | | | | | 0.12* |
| TMB | -30 | | -12 | | | 44 | | | 0.21† |
| WF | -35 | | | | | 23 | | | 0.12* |

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.0001$.

§ $p < 0.001$.

TABLE 2
Multiple regressions of EEG power on serum iron separately
for each frequency band and recording condition
significant ($p < 0.05$) models only

| Frequency task | Regression coefficients | | | | | | | | |
|----------------|-------------------------|----|-----|----|----|------|----|------|----------------|
| | Channel | | | | | | | | |
| | F3 | F4 | T3 | T4 | P3 | P4 | O1 | O2 | R ² |
| δ | | | | | | | | | |
| DSF | | | -36 | | | | 55 | -64 | 0.17* |
| DSB | -65 | 46 | | | | | 77 | -102 | 0.25† |
| TMF | | | | | | | 41 | -70 | 0.11* |
| TMB | -71 | 61 | | | | 72 | | -62 | 0.19* |
| S2 | -127 | 71 | | | | | | | 0.22† |
| θ | | | | | | | | | |
| S2 | | | | 56 | | -174 | | 96 | 0.17* |
| α | | | | | | | | | |
| R | | | | 64 | | -49 | | | 0.12* |
| IMG | | | | 59 | | -26 | | | 0.12* |
| WF | 53 | | | | | -66 | 23 | | 0.16* |
| $\beta 1$ | | | | | | | | | |
| $\beta 2$ | | | | | | | | | |
| IMG | | 38 | | | | | | | 0.10* |
| $\beta 3$ | | | | | | | | | |
| TMF | -48 | 33 | | | | | | | 0.14* |

* $p < 0.05$.

† $p < 0.01$.


These findings suggest that cognitive ability is related to iron nutriture in a way that is consistent with the asymmetries found in the EEG predictions of the iron indices: both the activation and the cognitive performance of the left hemisphere are related to iron status. Although the EEG findings are not as consistent for the right hemisphere, they are still generally congruent with the cognitive data: lower right hemisphere electrophysiologic activation (with the exception of the occipital lobe) and poorer nonverbal cognitive performance were associated with higher levels of iron stores. The third leg of the triangle relating iron status, brain electrophysiology, and cognition describes the relations between the EEG data and cognitive performance. Although too extensive to report here, these analyses indicated that left hemisphere activation (decreased power) was significantly predictive of shorter response latency for the word fluency task. Thus left hemisphere electrophysiological activation is relevant to verbal cognition,

and may mediate the relation between iron status and cognitive performance.

Iron status and thyroid function

The mean thyroid stimulating hormone level for this sample was 4.07 μ IU/ml (SD = 1.7). The mean for triiodothyronine was 135.4 ng/ml (SD = 41.2) and the mean for thyroxine was 8.0 ng/ml (SD = 2.9). Under the hypothesis that thyroid activity mediates the apparent relation between EEG measures and iron status it would be expected that serum ferritin or iron levels would be closely related to thyroid activity. The canonical correlation between iron status (serum iron, ferritin) and thyroid (thyroid stimulating hormone, triiodothyronine, thyroxine) variables showed no significant association between iron status and thyroid function in this sample. Similarly, zero-order correlations between the individual iron status measures and the thyroid variables were low and nonsignificant.

greater need for the biochemical substrate supporting that hemisphere's operations. In that case, iron nutriture would be the dependent variable in the equation, with the individual's biochemical characteristics dictating the iron requirement.

Although there are a number of issues that must be better understood to explain the connection between iron nutriture and brain function, the present study provides further evidence that the level of body iron, and by implication brain iron, is associated with qualitatively specific aspects of brain electrophysiology that are in turn important to cognitive function. Clarification of the implications of these relationships for persons with iron deficiency and for persons judged iron adequate by usual standards awaits further research. 

The authors thank Bruce Sawler for technical support, Sharon Shade and Elizabeth Lucas for data collection, Sandy Gallagher for clinical chemistries, Tom Bair for systems programming, and the students of the University of North Dakota who participated in this research.

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